REMARKS

Claims 1-3, 8-17, 22-33 and 35-37 are pending in this application.

Because this Request for Reconsideration does not contain any amendment adding any new matter to the application or any new argument that would require additional search or examination, entry of the Request is respectfully requested.

Claim Rejection – 35 U.S.C. § 103

The Office Action contains only an obviousness rejection. Claims 1-3, 8-14 and 35-37 were rejected under 35 U.S.C. § 103(a) as being unpatentable over European Patent Publication No. EP0610138 ("Godard"), "Recent Advances in Electrophilic Fluorination" (Taylor et al., Tetrahedron, 55 (1999), 12431-12477, hereafter referred as "Taylor") and "Comparison of Commercially Availabel Reagents for Luorination of Steroid 3,5-Dienol Acetates" (Reydellet-Casey et al., Organic Process and Research, 1997, 1, 217-221, hereafter referred as "Reydellet-Casey").

The claims are rejected for the same reasons in view of the same prior art references as that stated in the Office Action dated September 10, 2009. In particular, the Examiner states that Taylor teaches electrophilic fluorinating agents. Godard teaches process of preparing 6-fluorinated steroid. Reydellet-Casey teaches agent to introduce fluorine at 6-position of the steroid skeleton and discloses N-fluorobenzenesulfonimide (NFSI). The Examiner believes that it would have been obvious to one skilled in the art to prepare 6-alpha-fluorosteroids at the time the invention was made, because the references teach the fluorination with N-fluorobenzenesulfonimide and other agents and one skilled in the art would know how to select fluorinating reagent to prepare stereo selective 6-alpha-fluorosteroids based on prior art available at the time the invention was filed. In the pending Office Action, the Examiner states that the obviousness rejection is maintained because the Applicants' previous arguments are partially found persuasive. The Examiner has invited the Applicants to call the Examiner to discuss the remaining issues in this application to speed up the prosecution.

Applicants appreciate the time and effort of the Examiner spent on a telephone interview with the undersigned representative on September 9, 2010. During that interview, Applicants representative restated Applicants' position that the pending claims are not obvious over the

cited prior art references, thus are patentable, for at least the reasons detailed in the response filed March 10, 2010. Unfortunately, the Examiner needed more time to review the file before any agreement in terms of the patentability could be reached. Accordingly, Applicants hereby resubmit the previous arguments against obviousness, with a petition for one month extension of time.

Applicants respectfully submit that the cited references, alone or in combination, do not render the presently claimed process obvious at least because the references do not teach or suggest the use of a **novel** silyl enol derivative of formula (IV) as a starting material and the use of N-fluorosulfonamides or N-fluorosulfonimides as an electrophilic fluorinating reagent to obtain a highly stereoselective 6-alpha-fluorpregnane of formula (I). The presently claimed invention relates to a process for introducing a fluorine atom in position 6 of the steroid backbone stereoselectively in alpha. This is achieved by fluorination of a **novel** starting material, i.e., a compound of formula (IV) that contains 3-silyl enol ether pregnadiene, with an electrophilic fluorinating reagent, N-fluorosulfonamides or N-fluorosulfonimides. As compared with the prior art processes, the presently claimed process has achieved high 6α/6β fluorine epimeric ratio with low production of impurities in a single step reaction. See Examples 2-10 and compare with Reference Examples 1-7.

Godard describes introducing fluorine in positions 6 and 9 of a steroid backbone. The introduction of fluorine in position 6 is electrophilic and in position 9 is nucleophilic. It preferably uses an enol ester as a starting material (page 4 line 22) and uses an electrophilic fluorinating reagent, preferably Selectfluor® (page 5, line 18). Nowhere does Godard mention that its process is stereoselective nor the ratio of the alpha/beta isomers made by its process. It also does not teach or suggest a compound of formula (IV) or a 6-alpha-fluorpregnane of formula (I), let alone of using the compound of formula (IV) as a starting material in a highly stereoselective synthesis process for the 6-alpha-fluorpregnane of formula (I).

The conditions described in Godard, Example 1 part D, were used in **Reference Example 2** of the present invention. As described in Reference Example 2, the obtained result was 33% 6-alpha isomer and 37% 6-beta isomer, demonstrating that the process of Godard is NOT stereoselective. By way of comparison, the presently claimed process has resulted in much higher stereoselectivity for the 6-alpha isomer, e.g., 92% 6-alpha isomer and 1% 6-beta isomer in

Example 2, 92% 6-alpha isomer and 4% 6-beta isomer in Example 3, 76% 6-alpha isomer and 1% 6-beta isomer in Example 4, etc.

Reydenet-Casey does not compensate for the defect of Godard. Reydenet-Casey discloses a process for introducing fluorine in position 6 stereoselectively in a two-step process: Step 1, reacting a starting material containing enol ester with an electrophilic fluorinating reagent, preferably Selectfluor®, to obtain an alpha and beta isomer mixture; and Step 2, balancing the mixture in an acid medium followed by selective crystallization to obtain the alpha- or beta- isomer. This two-step process is very different from the process recited in the present claims, which achieves high stereoselectivity in a single reaction step without selective crystallization.

Like Godard, Reydenet-Casey also does not teach or suggest a compound of formula (IV) or a 6-alpha-fluorpregnane of formula (I), let alone the use of the compound of formula (IV) as a starting material in a highly stereoselective synthesis process for the 6-alpha-fluorpregnane of formula (I). In fact, Reydenet-Casey teaches away from using NFSI as a fluorination agent. Reydenet-Casey teaches that Selectfluor® is the best reagent for fluorination of enol acetate. See page 219, para. 1 and page 220, para. 1. It concludes NFSI is NOT useful for its application, i.e., achieving fluorination in position 6 in alpha, because the yields obtained were modest and the selectivity was beta (page 220, lines 7-9).

Taylor also does not compensate for the defects of Reydenet-Casey and Godard. This general review of electrophilic fluorination discusses introducing fluorination in position 6 in steroids. See Section 6 at page 12451 to page 12455. In all schemes described in Section 6 of Taylor, a starting material different from a compound of formula (IV) or an electrophilic fluorinating reagent different from N-fluorosulfonamides or N-fluorosulfonimides was used and only alpha/ beta isomer mixtures or selectivity in beta were obtained. See, for example, the bridging paragraph on pages 12452 and 12453.

Like Godard and Reydenet-Casey, Taylor also does not teach or suggest a compound of formula (IV) or a 6-alpha-fluorpregnane of formula (I), let alone the use of the compound of formula (IV) as a starting material in a highly stereoselective synthesis process for the 6-alpha-fluorpregnane of formula (I). In fact, Taylor teaches away from using a compound containing silyl enol ether as a starting material, because impurities due to the introduction of fluorine in

position 4 were obtained and the beta isomer was preferably formed when a steroid containing silyl enol ether was used as a starting material in scheme 36 (page 12454, 1st para., especially line 5).

None of the cited prior art references, separately or as a whole, contains the technical features of the invention nor do they even contain teachings leading the person skilled in the art in the suitable direction to reach the solution provided by the invention. In view of the prior art references, a person skilled in the art would not have been motivated to use a silyl enol ether as a starting material with a reasonable expectation of success, because according to Taylor, a starting material with silyl enol ether resulted in impurities due to the introduction of fluorine in position 4 and beta isomer was preferably formed. The person skilled in the art would also not have been motivated to use NFSI for the electronegative fluorination with a reasonable expectation of success, because according to Reydenet-Casey, using NFSI as the fluorination agent resulted in limited yields and the selectivity in beta. The presently claimed invention cannot be considered a selection of the same type described in the prior art, because at no time does the prior art describe how to achieve alpha stereoselectivity by using the combination of the silyl enol derivatives of formula (IV) as starting materials and NFSI type electrophilic fluorinating reagent as recited in the present claims.

Only through innovative experimentation, Applicants discovered that using a silyl enol derivative of formula (IV) as a starting material and N-fluorosulfonamides or N-fluorosulfonimides as an electrophilic fluorinating reagent has resulted in highly stereoselective synthesis of 6-alpha-fluorpregnane of formula (I) with low impurity in a single step reaction. This superior result is highly unexpected from the prior art teaching and has solved a long time problem in the art.

Accordingly, reconsideration and withdrawal of the rejection of claims 1-3, 8-14 and 35-37 under 35 U.S.C. § 103(a) as being unpatentable over Godard, Taylor and Reydellet-Casey are respectfully requested.

Rejoinder of Other Claims

Upon finding claims 1 and 35 and their dependent claims allowable, Applicants respectfully request that the Examiner rejoin claims 15-17 and 22-33 for substantive examination

and find them allowable. Claims 15-17 and 22-25 are directed to the starting material, the silyl enol derivatives of formula (IV), recited in the process of claim 1. Claims 26-33 are directed to the process for obtaining the starting material of formula (IV), which is part of the process recited in claim 35. For reasons similar to that discussed above, Applicants respectfully submit that claims 15-17 and 22-33 are patentable because they are enabled by general disclosure and specific examples in the specification, and that they are not anticipated or rendered obvious by any of the prior art references.

It is respectfully submitted that the present application, including claims 1-3, 8-17, 22-33 and 35-37, is in condition for allowance and such action is respectfully solicited. Applicants appreciate the effort of the Examiner. If needed, the Examiner is invited to contact Applicants' undersigned attorney by telephone for the early issuance of a patent.

Respectfully submitted,

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